REMARKS

Claims 1, 4, 6, 12, 19-20, 30-31 and 33-35 have been amended, claims 5, 9-11, 21-28, 32 and 36-39 have been cancelled without prejudice to or disclaimer of the underlying subject matter, and claims 40-51 have been added. The application presently contains claims 1-4, 6-8, 12-20, 29-31, 33-35, and 40-51. Support for the amendments and the new claims may be found in the original claims and throughout the specification, *e.g.*, at page 5, line 20, through page 6, line 18; page 8, lines 6-22; page 11, lines 13-14; page 18, lines 14-16; page 21, lines 15-22; Table 6; and Figures 15 and 16. No new matter is presented by these amendments.

1. Response to Notice to Comply with Sequence Rules

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed on January 8th as part of Paper No. 14, Applicants submit herewith the following documents for appropriate action by the U.S. Patent and Trademark Office ("the Office"): (1) a copy of the Notice; (2) a substitute sequence listing in computer readable form and a paper copy of the substitute sequence listing; and (3) a Statement Regarding Sequence Submission. Support for the amendments may be found throughout the specification, for example at Table 1; and page 4, lines 2-6. The specification has also been amended to contain the incorporation of the Sequence Listing as required by 37 C.F.R. 1.821 *et seq*. No new matter is introduced by this submission.

2. Rejections under Obviousness-Type Double Patenting Doctrine

Claims 1, 5-6, 12, and 33 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 4-7 of U.S. Patent No. 6,455,673; and claims 1, 6, 8, 12, 15, 20, and 33 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-13 and 23-27 of U.S. Patent No. 5,917,017. Office Action at pages 3-4. Applicants respectfully traverse these rejections.

Contrary to the assertions made in the Office Action, the claims of the present application are not anticipated or made obvious by the '673 patent or the '017 patent. An obviousness-type double patenting rejection is analogous to an obviousness rejection under 35 U.S.C. § 103, and therefore requires a similar analysis. *See* MPEP § 804, at page 800-22 (8th ed.) (citations omitted). Applicants submit that neither cited patent teaches or suggests all of the claim limitations of the present application, as is required for obviousness and anticipation determinations. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Furthermore, the Office Action does not make clear why "a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is an obvious variation of the invention defined in a claim" of either the '673 patent or the '017 patent. *See* MPEP § 804, at page 800-22.

Claims 1, 5-6, 8, 12, 15, 20, and 33 of the present application each recite a B moiety of a pore-forming ***binary*** A-B toxin. The '673 patent and the '017 patent do not teach or suggest B moieties of a pore-forming ***binary*** A-B toxin. The '673 patent and the '017 patent discuss diphtheria toxin, which is not a binary A-B toxin. The present application defines a pore-forming binary A-B toxin as a "pore-forming A-B toxin in which the A and B moieties of the pore-forming toxin inhabit separate proteins, and interact during the intoxication of host cells." Specification at page 10, lines 1-4. Diphtheria toxin, however, consists of a single protein that is excreted from a bacterial cell after synthesis, and therefore is **not** a binary toxin. *See* '673 patent at col. 1, lines 16-42; Specification at page 9, lines 5-8. Because neither cited patent teaches or suggests all of the claim limitations of the present application, Applicants submit that the double patenting rejections over the '673 patent and the '017 patent are improper, and should be withdrawn.

Moreover, claims 1, 5-6, 8, 12, 15, 20, and 33 of the present application each recite a B moiety that comprises a mutation that inhibits its pore-forming ability. The '673 patent and the '017 patent are silent on whether any of the mutations disclosed therein ***necessarily*** inhibit the pore-forming ability of a B moiety. It is well-established patent jurisprudence that when a reference is silent about an alleged inherent characteristic, in this instance inhibition of pore-forming ability, the Office must provide evidence to "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. U.S.A. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). The Office has not provided any evidence showing that the missing descriptive matter is necessarily present in the '673 patent or the '017 patent.

Moreover, obviousness-type double patenting requires the application claims to be "an obvious variation of the ***invention defined in a claim*** in the patent." MPEP § 804, at page 800-23, *citing In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998) (emphasis added). The Office has not provided argument in support of why a person of ordinary skill would find the claims of the present application obvious over the '673 or '017 patent ***claims***. The Office cites to a portion of the specification of the '673 patent, but provides no argument or explanation as to why the '673 or the '017 patent claims allegedly render the present claims obvious, either expressly or inherently. Accordingly, Applicants submit that the double patenting rejections over the '673 patent and the '017 patent are improper, and should be withdrawn.

3. Written Description Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 1-3, 5-8, 12-18, 20, 29-31 and 33-35 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in a manner that reasonably conveys to one of ordinary skill in the art that

the inventors had possession of the claimed invention at the time of filing. Office Action at pages 5-8. Applicants respectfully disagree and assert that the claims meet the written description requirement.

The purpose of the written description requirement is simply to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 U.S.P.Q.2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996). In accordance with this purpose, Applicants need not "describe," in the sense of Section 112, all things that are encompassed by the claims. To contend otherwise would contradict established jurisprudence, which teaches that a patent may be infringed by technology developed after a patent issues. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251, 9 U.S.P.Q.2d 1461, 1464 (Fed. Cir. 1989).

A related and equally well-established principle of patent law is that claims "may be broader than the specific embodiment disclosed in a specification." *Ralston Purina Co. v. Far-mor-Co*, 772 F.2d 1570, 1575, 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985), quoting *In re Rasmussen*, 650 F.2d 1212, 1215, 211 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Thus, simply because the claimed B moiety comprising a mutation that inhibits its pore-forming ability may be a B moiety from any pore-forming binary A-B toxin does not require that Applicants describe each and every pore-forming binary A-B toxin. Applicants respectfully point out that "... representative compounds may provide an implicit description on which to base generic claim language." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d (B.N.A.) 1614, 1618 (Fed. Cir. 1989).

Applicants have provided detailed chemical structures, *i.e.*, sequences from B moieties comprising mutations that inhibit their pore-forming ability, including SEQ ID

NOs: 1-18. *See, e.g.*, Specification at Table 1; Sequence Listing. These sequences provide "structural features possessed by members of the [claimed] genus that distinguish[] them from others." *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). Moreover, contrary to the Office's assertions, Applicants ***have*** provided description of how mutant B moieties in pore-forming binary A-B toxins other than anthrax protective antigen (PA) would be constructed. *See, e.g.*, Specification at Table 6; pages 44-46 (description of mutations in toxins from *Clostridium difficile, C. perfringens, C. spiroforme*, etc.); page 21, line 14 through page 22, line 4 (description of residues that can be mutated to affect pore-formation in several toxins); Figures 15 & 16 (alignments highlighting invariant amino acids among toxins which can be mutated to affect pore-formation). Applicants respectfully point out that the Office's argument based on a cytotoxin from phage ΦCTX of *Pseudomonas aeruginosa* is inapplicable to the claimed invention as the *P. aeruginosa* cytotoxin is not a pore-forming binary A-B toxin. Accordingly, in the present case, Applicants have provided detailed chemical structures in contrast to the mere name cDNA provided in *Eli Lilly*. Therefore, the present claims meet the written description provision under 35 U.S.C. § 112, first paragraph.

Applicants not only provide specific structural features of the claimed invention, namely exemplary B moieties, but Applicants also provide methods for generating mutations in a B moiety, specification at pages 23-25, and methods for assaying whether the mutated B moieties have inhibited pore-forming ability, *e.g.*, methods of assaying cell surface translocation, LFnDTA toxicity, or rubidium release, as described at pages 25-31 of the specification. Therefore, contrary to the Office's assertions, Applicants have described B moieties comprising mutations that inhibit pore-forming ability, and means of testing the pore-forming abilities of B moieties. For the foregoing reasons, Applicants submit that one of ordinary skill in the art must recognize that at the time of filing Applicants were in possession of the claimed invention.

Indeed, Applicants disclose sequences that encode the claimed B moieties, *e.g.*, at least SEQ ID NOs: 1-12, which are B moieties from anthrax protective antigen (PA), comprising mutations that inhibit their pore-forming ability. Moreover, Applicants respectfully draw the Office's attention to the fact that "...it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). Thus, in the present case, Applicants assert that the disclosure of at least twelve mutant anthrax protective antigens, in combination with "other appropriate language" in fact does provide sufficient written description for claims within the genus. In the present case, such "other appropriate language" includes the form of percent sequence identity, the location of the claimed mutations, and an assay by which inhibition of pore-forming activity can readily be confirmed. Therefore, it is clear that one of ordinary skill in the art would recognize that Applicants were in possession of B moieties comprising mutations that inhibit their pore-forming ability.

With respect to claim 6 and its dependents, and claims 33-35, which recite vaccine compositions, Applicants describe exemplary B moieties of vaccine compositions, and dominant negative PA mutants or fragments thereof, which can induce the production of protective antibodies and inhibit the activity of PA. *See* Specification at page 18, line 12 through page 20, line 7; page 22, line 19 through page 23, line 4; Table 1. Furthermore, contrary to the Examiner's assertions, Applicants ***have*** described B moieties which induce protective immune responses, e.g., a ΔD2L2 mutant, a K397D + D425K double mutant, and an F427A mutant. These exemplary mutants exhibit little or no diminution of immunogenicity relative to wild-type PA in rats, and when administered proved protective against anthrax infection in a rat model. Specification at page 22, lines 22-26; pages 37-41; Tables 4 and 5.

With respect to claim 12 and its dependents, which recite B moieties that inhibit the pore-forming ability of a naturally-occurring B moiety of the same toxin, Applicants describe exemplary B moieties in the specification. *E.g.*, Specification at pages 31-41; Examples 6 and 7 entitled "Inhibition of wild-type PA pore formation by PA mutants" which detail inhibition of the pore-forming ability of a naturally-occurring B moiety *in vitro*; Example 9, entitled "Toxin inhibition *in vivo*" which details inhibition *in vivo*. *See also* Tables 3, 4, and 5.

Accordingly, for the foregoing reasons, the written description rejections under 35 U.S.C. §112, 1st paragraph, are incorrect and should be withdrawn.

4. Enablement Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 6-8 and 33-35 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification because the claimed invention allegedly does not "provide enablement for the use of any mutant toxin (protein or polypeptide) as a pharmaceutical composition (vaccine)." Office Action at page 8. Applicants respectfully traverse these rejections.

The specification discloses evidence, in the form of a working example, that the claimed B moiety vaccine compositions induce a protective immune response in vaccinated rats that enables rats to survive injection with lethal doses of anthrax toxin. Specification at pages 39-40 and Table 5. It is well-established law that "the enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins University v. CellPro*, 152 F.3d 1342, 1361, 47 U.S.P.Q.2d 1705, 1719 (Fed. Cir. 1998) (emphasis added), quoting *Engel Indus. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 U.S.P.Q.2d 1300, 1304 (Fed. Cir. 1991). Accordingly, Applicants submit that the specification does enable the claimed invention.

The Office has provided neither specific evidence supporting the rejection nor any explanation of why the specification allegedly fails to enable. *See In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *Ex parte Lemak*, 210 U.S.P.Q. 306, 307 (Bd. App. 1981) ("pure conjecture" does not substantiate rejection for lack of enablement). The Office states that undue experimentation would be required to make and use the invention as it is claimed. Office Action at pages 9-10. Applicants respectfully disagree.

A specification that discloses how to use a claimed invention "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995), quoting *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in original). The Office has failed to provide a reason to doubt the objective truth of Applicants' specification.

The Office relies on multiple citations in support of its assertion that formulation and use of a successful vaccine would require undue experimentation without a prior demonstration of vaccine efficacy. Office Action at page 9. However, the Office fails to acknowledge the teachings set forth in the specification, for example, teaching of the amino acids of other B moieties that correspond to the mutated B moieties of anthrax, and teaching that random mutations may be produced in pore-forming toxins and screened in standard assays to determine whether they inhibit pore-forming ability (*e.g.*, by assaying cell surface translocation, LFnDTA toxicity, or rubidium release). Specification at pages 44-46; Figures 15 and 16; Table 6; page 11, lines 19-24; and pages 25-31. Desirable mutants identified by these methods may be further characterized in well-known animal models. Specification at page 46, lines 9-11; page 48, lines 7-10. Thus, one skilled in the art, reading the specification, can identify those B moieties having mutations that inhibit

their pore-forming ability and that induce a protective immune response in a vaccinated animal.

The Office contends that without a "prior demonstration of vaccine efficacy", it would require undue experimentation to formulate and use a successful vaccine. Office Action at page 9. To the extent that the Office is suggesting there is a requirement for precise *a priori* predictability without recourse to any experimentation, that position is without legal support. *Cf. Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984) ("[t]hat some experimentation is necessary does not preclude enablement"). The proper test of enablement in such a situation is whether the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *See In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991).

The Office's "test", however, would apparently require the art worker to be able, without even entering a laboratory, to name particular mutant B moieties that are effective vaccines. However, that is not the *Vaeck* test. Under the *Vaeck* test, the specification is enabling if it "adequately guide[s] the art worker to determine, without undue experimentation, which [particular B moieties] among all those encompassed by the [group of B moieties comprising mutations inhibiting their pore-forming ability] possess [vaccinic efficacy]." *In re Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2d at 1445. The Vaeck test recognizes proper enablement where the skilled art worker is able to determine, once a particular B moiety has been selected from the group and based on a reasonable experiment, whether that particular B moiety has vaccinic efficacy.

The high level of skill in the art, the extensive knowledge available to one of skill in the art, and the teachings of the present specification adequately guide the art worker to determine, after selection and without undue experimentation, which B moieties

encompassed by the claims possess the disclosed utilities. Performing routine and well-known steps cannot create undue experimentation even if it is laborious. *See In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404; *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-19 (C.C.P.A. 1976).

Based on the foregoing, Applicants submit that the enablement rejections under 35 U.S.C. § 112, first paragraph, are incorrect and should be withdrawn.

5. *Indefiniteness Rejections under 35 U.S.C. § 112, 2nd paragraph*

Claims 4, 5, 19-20, 30-31, and 34-35 are rejected under 35 U.S.C. §112, 2nd Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Office Action at page 10. Applicants respectfully disagree and traverse the rejections.

Claims 4 and 19 were rejected because they "recite abbreviations that are unclear", particularly the term "ΔD2L2". The Office asserts that "abbreviations in the claims [are] permitted upon definition of the term at their first appearance in the claims." Office Action at page 10. Applicants respectfully disagree.

Applicants respectfully point out that the claims are to be read in light of the specification. *See In re Vogel*, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970). The meaning of the term "ΔD2L2" used in these claims (through their dependency on new claims 50 and 51, respectively) is clear when read in light of the specification, which the Office admits (on page 11 of the Office Action) defines this term. In view of the definition provided in the specification, and the clear guidance provided in the MPEP with respect to claim terminology, Applicants submit that use of the term "ΔD2L2" does not render claims 4 and 19 indefinite, and that the rejection of these claims should be withdrawn. *See* MPEP § 608.01(o) (8th ed., Aug. 2001) ("The meaning of every term used in any of the claims should be apparent from the descriptive portion of

the ***specification***...") (emphasis added); MPEP § 2173.05(a) (8th ed., Rev. 1, Feb. 2003): "When the ***specification*** states the meaning that a term in the claim is intended to have, the claim is examined using that meaning.... *In re Zletz*, 893 F.2d 319, 13 USPT2d 1320 (Fed. Cir. 1989)" (emphasis added).

Claims 4 and 19 also stand rejected as improperly broadening the scope of their respective base claims. Office Action at pages 10-11. Applicants disagree with this rejection, and submit that present claims 4 and 19 do not broaden the scope of their base claims. Present claims 4 and 19 recite ΔD2L2 (through their dependency on new claims 50 and 51, respectively) only in ***combination*** with other mutations, and thereby when read by one of skill in the art would be understood to recite a ΔD2L2 mutation ***in addition to*** a mutation that inhibits pore-forming ability that is ***not in*** the D2L2 loop. Applicants submit that these claims do not improperly broaden the scope of their base claims, as the claim term "comprises" leaves the claims open to further elements.

Claim 5 has been cancelled, rendering its rejection moot.

Claims 20 and 30 stand rejected as improperly broadening the scope of their respective base claims. Office Action at page 11. Although Applicants disagree with these rejections, in order to facilitate prosecution Applicants have amended claims 20 and 30 to "further comprise" their respective deletions, thereby obviating the rejections. Furthermore, Applicants submit that the rejection for lack of antecedent basis is improper, because present claims 20 and 30 are dependent on base claims that recite pore-forming binary A-B toxins, which are described in the specification (e.g., Table 6) as comprising a D2L2 loop or its equivalent. *See* MPEP § 2173.05(e) (8th ed., Rev. 1, Feb. 2003): "For example, the limitation 'the outer surface of said sphere' would not require an antecedent recitation that the sphere has an outer surface." One of skill in the art would clearly understand a pore-forming binary A-B toxin to comprise a D2L2 loop or its equivalent, therefore there is no lack of antecedent basis.

Claims 31, 34 and 35 were rejected for reciting conditional claim limitations. In order to facilitate prosecution Applicants have amended the claims to clarify that the B moiety is anthrax protective antigen. Accordingly, the rejection has been obviated.

Based on the foregoing, Applicants submit that the indefiniteness rejections under 35 U.S.C. § 112, second paragraph are incorrect and should be withdrawn.

6. Rejections under 35 U.S.C. § 102

Claims 1-8, 12-20, 29-31, and 33-35 were rejected under 35 U.S.C. §102 as being allegedly anticipated by six different references. Office Action at pages 12-15. However, in order to support an anticipation rejection under 35 U.S.C. §102, the Office must demonstrate that each and every element of a claimed invention is disclosed within a single prior art reference. *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990). Indeed, the reference must describe an applicant's claimed invention sufficiently to have placed a person of ordinary skill in the art in the field of the invention in possession of it. *See In re Paulson,* 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994). The Office has not demonstrated that any of the cited references teaches each and every element of the claimed invention, and therefore the anticipation rejections are improper and should be withdrawn.

Collier et al. (U.S. Patent No. 5,917,017)

Claims 1, 5-6, 8, 12, 14-15, 20, and 33 were rejected under 35 U.S.C. §102 (e) as being allegedly anticipated by Collier *et al.* (U.S. Patent No. 5,917,017) (hereinafter "the '017 patent"). Office Action at page 12. The Office alleges that claims 1, 5-6, 8, 12, 14-15, 20, and 33 are inherently anticipated by the alleged disclosure in the '017 patent of a B moiety of a pore-forming binary A-B toxin which comprises a mutation that inhibits its

pore-forming ability. Office Action at pages 12-13. Applicants respectfully traverse this rejection.

Claims 1, 5-6, 8, 12, 14-15, 20, and 33 of the present application each recite a B moiety of a pore-forming ***binary*** A-B toxin. The '017 patent does not teach or suggest B moieties of a pore-forming ***binary*** A-B toxin. The '017 patent discusses diphtheria toxin, which is not a binary A-B toxin. The present application defines a pore-forming binary A-B toxin as a "pore-forming A-B toxin in which the A and B moieties of the pore-forming toxin inhabit separate proteins, and interact during the intoxication of host cells." Specification at page 10, lines 1-4. Diphtheria toxin, however, consists of a single protein that is excreted from a bacterial cell after synthesis, and therefore is **not** a binary toxin. *See* '673 patent at col. 1, lines 16-42; Specification at page 9, lines 5-8.

Moreover, the rejected claims of the present application each recite a B moiety that comprises a mutation that inhibits its pore-forming ability. The '017 patent is silent on whether any of the mutations disclosed therein ***necessarily*** inhibit the pore-forming ability of a B moiety. It is well-established patent jurisprudence that when a reference is silent about an alleged inherent characteristic, in this instance inhibition of pore-forming ability, the Office must provide evidence to "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. U.S.A. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). The Office has not provided any evidence showing that the missing descriptive matter is necessarily present in the '017 patent.

Accordingly, the failure of the '017 patent to teach a B moiety of a pore-forming binary A-B toxin comprising a mutation that inhibits its pore-forming ability renders it defective as an anticipatory reference. Because the '017 patent does not teach all of the

claim limitations of the present application, Applicants submit that the anticipation rejection of claims 1, 5-6, 8, 12, 14-15, 20, and 33 is improper, and should be withdrawn.

Johnson et al. (U.S. Patent No. 5,792,458)

Claims 1, 3, 5-6, 8, 12, and 33 were rejected under 35 U.S.C. §102 (b) as being allegedly anticipated by Johnson *et al.* (U.S. Patent No. 5,792,458) (hereinafter "Johnson"). Office Action at page 12. The Office alleges that claims 1, 3, 5-6, 8, 12, and 33 are anticipated by the alleged disclosure in Johnson of a B moiety of a pore-forming binary A-B toxin which comprises a mutation that inhibits its pore-forming ability. Office Action at page 13. Applicants respectfully traverse this rejection.

Claims 1, 3, 5-6, 8, 12, and 33 of the present application each recite a B moiety of a pore-forming ***binary*** A-B toxin. Johnson does not teach or suggest B moieties of a pore-forming ***binary*** A-B toxin. Johnson discusses diphtheria toxin and ricin toxin, neither of which are binary A-B toxins. *See* Johnson at col. 2, lines 32-39 ("Ricin and diphtheria toxins are 60,000 to 65,000 dalton proteins..."). Pore-forming binary A-B toxins are toxins in which "the A and B moieties of the pore-forming toxin inhabit ***separate proteins***, and interact during the intoxication of host cells." Specification at page 10, lines 1-4 (emphasis added). Diphtheria toxin and ricin toxin, however, each consist of a single protein that is excreted from a bacterial cell after synthesis, and therefore neither is a binary toxin.

Accordingly, the failure of Johnson to teach a B moiety of a pore-forming binary A-B toxin comprising a mutation that inhibits its pore-forming ability renders it defective as an anticipatory reference. Because Johnson does not teach all of the claim limitations of the present application, Applicants submit that the anticipation rejection of claims 1, 3, 5-6, 8, 12, and 33 is improper, and should be withdrawn.

Cirino et al., Singh et al., and Miller et al.

Claims 1-4, 6-8, 12-13, 15, 19-20, 29-31, and 33-35 were rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Cirino *et al.* (U.S. Patent No. 6,329,156) (hereinafter "Cirino"); claims 1-3, 5-8, 12-18, and 31 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Singh *et al.* (*Journal of Biol. Chemistry* 269(46):29039-29046) (hereinafter "Singh"); and claims 1-4, 6-8, 12-20, 29-31, and 33-35 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Miller *et al.* (Protein Science 7(1):175, abstract number 712-M) (hereinafter "Miller"). Office Action at pages 13-15. The Office alleges that the claims are anticipated by the alleged disclosure in Cirino, Singh and Miller of a B moiety of a pore-forming binary A-B toxin which comprises a mutation that inhibits its pore-forming ability. *Id.* Applicants respectfully traverse these rejections.

Claims 1-8, 12-20, 29-31, and 33-35 of the present application each recite a B moiety of a pore-forming binary A-B toxin comprising a mutation that inhibits its pore-forming ability, wherein said mutation is ***not*** a mutation of Phe313, Phe314, or Asp315 of anthrax protective antigen. None of the cited references teach a mutation that inhibits pore-forming ability that is ***not*** a mutation of Phe313, Phe314, or Asp315. Because none of the cited references teach all of the claim limitations, the anticipation rejections of claims 1-8, 12-20, 29-31, and 33-35 are improper and should be withdrawn.

Cirino discusses anthrax toxin and fragments of the B moiety of anthrax (protective antigen), and specifically a PA32 fragment. *See* Cirino at col. 2, line 24 through col. 4, line 33. Cirino teaches a mutation in the PA32 fragment whereby PA32 "is unable to form pores due to the absence of the D2L2 loop of domain 2." Cirino at col. 10, ll. 59-67. Accordingly, because the mutation in Cirino's PA32 fragment that inhibits its pore-forming ability is a mutation of Phe313, Phe314, or Asp315 (a deletion mutation of these residues in the D2L2 loop), Cirino does **not** teach a mutation that inhibits pore-

forming ability that is not a mutation of Phe313, Phe314, or Asp315. Accordingly, Cirino is defective as an anticipatory reference because it does not teach all of the claim limitations of the present application, and the anticipation rejection of claims 1-4, 6-8, 12-13, 15, 19-20, 29-31, and 33-35 should be withdrawn.

Singh discusses anthrax toxin and fragments of the B moiety of anthrax (protective antigen), and specifically anthrax protective antigen having mutations in the D2L2 loop, particularly residues 313-315. Singh also teaches that mutations in residues 313-315 inhibit the pore-forming ability of anthrax protective antigen. Singh at page 29046, col. 1. Singh does not teach, however, a mutation in anthrax protective antigen that inhibits pore-forming ability that is ***not*** a mutation of Phe313, Phe314, or Asp315. Accordingly, Singh is defective as an anticipatory reference because it does not teach all of the claim limitations of the present application, and the anticipation rejection of claims 1-3, 5-8, 12-18 and 31 should be withdrawn.

Miller discusses anthrax protective antigen having a mutation in the D2L2 loop, particularly residues 302-324. Miller does not teach, however, a mutation in anthrax protective antigen that inhibits pore-forming ability that is ***not*** a mutation of Phe313, Phe314, or Asp315 (which as residues 313, 314, and 315 are included in the Miller mutation of residues 302-324). Moreover, it is well-established patent jurisprudence that when a reference is silent about an alleged inherent characteristic the Office must provide evidence to "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. U.S.A. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991). The Office has not provided any evidence showing that the missing descriptive matter is necessarily present in Miller. Accordingly, Miller is defective as an anticipatory reference because it does not teach all of the claim

limitations of the present application, and the anticipation rejection of claims 1-4, 6-8, 12-20, 29-31 and 33-35 should be withdrawn.

Collier et al. (PCT Publication No. WO99/42473)

Claims 1-3, 5-8, 12-18, 29, 31, and 33-35 were rejected under 35 U.S.C. §102(a) as being allegedly anticipated by Collier *et al.* (PCT Publication WO99/42473) (hereinafter "the '473 application"). Office Action at page 15. Applicants respectfully request that the rejection be withdrawn because Applicants have shown in the Declaration of John Collier that any description of the above-referenced invention in WO 99/42473 was the contribution of John Collier alone, notwithstanding the inclusion of the additional inventors. Erika L. Benson and Alan Finkelstein, co-inventors on WO 99/42473, contributed only to point mutations in anthrax protective antigen that are not claimed in U.S.S.N. 09/848,909. Accordingly, the rejection is now moot, and should be withdrawn.

CONCLUSION

It is believed that the present claims are in immediate condition for allowance. Accordingly, Applicants respectfully request that the Examiner pass the application to issue.

Enclosed is a petition to extend the period for replying for one month, to and including May 8, 2003. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: May 8, 2003

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